37. (new) The transgenic mouse of claim 35, wherein said mouse is a knock-out mouse created by homologous recombination.

REMARKS

Claims 14-20 are pending in the application. Claims 14-17 and 20 are withdrawn from consideration, as drawn to non-elected subject matter. Applicants expressly reserve the right to timely file a divisional application directed to the non-elected subject matter. Claims 18 and 19 are rejected.

The Examiner objected to claims 18 and 19 as being dependent upon a non-elected base claim 15. Applicants have cancelled claims 18 and 19, and re-presented them as new independent claims 21 and 29. Applicants submit that claims 21 and 29 are commensurate with the scope of claims 18 and 19 (and claim 14) as they define additional steps which are an extension of the novel method claimed. No new matter is introduced by the new claims.

Support for new claims 21-37 can be found in the specification as filed, for example, in original claims 14, 18 and 19; Examples 2 and 4; page 6, lines 21-24; page 10, lines 21-27, page 12, lines 19-21; on page 13, lines 8-27, and elsewhere throughout the specification.

REJECTION OF CLAIMS UNDER 35 USC §101

Claims 18 and 19 are rejected under 35 U.S.C. §101. The Examiner contends that claims 18 and 19 are not directed to statutory subject matter, and that it is PTO policy not to issue claims that encompass humans. According to the Examiner,

the rejection may be overcome by inserting "non-human" before "mammals" or "embryos".

In reply, Applicants submit that the Examiner's rejection is rendered moot by the amendments to the claims. Specifically, claims 18 and 19 have been cancelled, and newly added claims 21-37 recite "non-human" before "mammals" or "embryos". Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

REJECTION OF CLAIMS UNDER 35 USC §112, FIRST PARAGRAPH

Claims 18 and 19 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner describes the nature of the invention as a method of cloning, manipulating and performing mutagenesis of defined segments of DNA having flanking sequences using site-specific targeting, and subsequently generating knock-in or knock-out mammal. Second, the Examiner contends that the claims are very broad, and encompass a method of cloning, manipulation of any seqment of DNA and making any type of knock in or knock-out non-human mammal, and transgenic embryo by using DNA generated by the recited cloning method. Third, the Examiner contends that the amount of guidance and working examples in the specification is limited, and that the specification does not provide any method steps for making such knock-in or knock-out animals and transgenic embryos, other than production of knock–in or knock-out mice by homologous recombination in

embryonic stem cells. The Examiner concludes that one skilled in the art would have to turn to prior art for guidance to make and use the transgenic mammal as claimed, and that the state of the art at the time of filing only taught the generation of knock-in or knock-out mice by homologous recombination.

The Examiner also contends that since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem cell must be available to carry out the method. According to the Examiner, the only species in which the ES cell is available is the mouse (citing, Bradley *et al.* (1992) at paragraph bridging 537-538; Campbell and Wilmut (1997) at p.65; and Mullins *et al.* (1996) at p. 1558, column 2, paragraph 1.). The Examiner concludes that because no knock-out mammals could be made for any species other than the mouse at the time of filing, the invention is enabled for a knock-in or knock-out mouse generated by using ES cells.

In response, Applicants respectfully disagree. First, Applicants submit that the Examiner's rejection is rendered moot by the cancellation of claims 18 and 19, and the addition of new claims 21-37. Second, Applicants disagree with the Examiner's contention that at the time the present application was filed the prior art only taught the generation of transgenic mammals by homologous recombination. Specifically, Applicants submit that at the time of filing there were numerous techniques available and well-known in the art for integrating DNA into the genome of a mammal to make a transgenic animal. Those techniques included, but were not limited to, microinjection, chemical transfection, homologous recombination, electroporation, and the production

of chimeras. Applicants submit that the articles cited by the Examiner provide evidence of this point. For example, page 2 of Campell and Wilmut describe three such technologies: pronuclear injection, production of chimeras, and production of single genotype animals. Mullins and Mullins describe on pages 1-2 the production of transgenes in rats by pronuclear injection and chimeric methods. Therefore, Applicants submit that the invention as described and claimed in the present application is not limited to the production of transgenic mammals by homologous recombination, but instead, encompasses all of the common methods well known to those skilled in the art at the time of filing for integrating DNA into the genome a mammal.

In view of the amendments and remarks described above, Applicants respectfully request that the Examiner withdraw this rejection.

REJECTION OF CLAIMS UNDER 35 USC §112, SECOND PARAGRAPH

Claims 18 and 19 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and disctinctly claim the subject matter which the applicant regards as the invention. According to the Examiner, the claims are drawn to a method of cloning, manipulating and performing mutagenesis of defined segments of DNA. However, the Examiner contends that the recitation of "further comprising the step of using the defined segment of DNA to create knock-in or knock-out strains of mammals/transgenic embryos" renders the claims indefinite because it is unclear what kind of method the claims encompass. In addition, the Examiner argues it is unclear whether the final product is the "defined segment of DNA" or "knock-in or knock-out mammals/transgenic embryos". The Examiner also contends

that the recitations of "stains of mammals" and "embryos" also render the claims indefinite because it is unclear how many mammals and embryos the claims encompass, and suggests to use singular terms.

Finally, the Examiner argues that claims 18 and 19 provide for the use of "defined segment of DNA", but that since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. The Examiner states that a claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. The Examiner further rejected claims 18 and 19 under 35 USC 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 USC 101.

In reply, Applicants respectfully submit that the Examiner's rejections of the claims are rendered moot by the amendments to the claims. Claims 18 and 19 have been cancelled. New claims 21-37 have been presented to address each of the Examiner's indefiniteness rejections. In addition, Applicants submit that the Examiner's rejection of claims 18 and 19 under 35 U.S.C.§101 has also been overcome by the newly presented claims, as the new claims more clearly recite the steps for producing the transgenic mammals/embryos of the invention.

It is respectfully submitted that the above amendments and remarks put the claims in condition for allowance. Early and favorable action by the Examiner is solicited.

AUTHORIZATION

No additional fee is believed to be necessary. However, the Commissioner is hereby authorized to charge any additional fee(s) which may be required for this response, or to credit any overpayment to Deposit Account No. 13-4500, Order No. 4167-4000.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 4167-4000. A DUPLICATE OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Date: May 19, 2003

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